CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074549

Trade Name : KETAMINE HCL INJECTION

Generic Name: Ketamine HCL Injection 50mg/ml and 100mg/ml

Sponsor : Sanofi Winthrop, Inc.

Approval Date:June 27, 1996

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074549

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	Included	Pending Completion	Not Prepared	Not Required
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Medical Review(s)				
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EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
Administrative Document(s)				
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074549

APPROVAL LETTER

ANDA 74-549

JUN 27 1996

Sanofi Winthrop, Inc.
Attention: Gregory M. Torre, Ph.D., J.D.
90 Park Avenue
New York, NY 10016

Dear Sir:

This is in reference to your abbreviated new drug application dated September 30, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Ketamine Hydrochloride Injection USP, 50 mg base/mL(10 mL vial) and 100 mg base/mL(5 mL vial).

Reference is also made to your amendments dated April 19 and May 28, 1996.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Ketamine Hydrochloride Injection USP, 50 and 100 mg base/mL to be bioequivalent and, therefore, therapeutically equivalent to the listed drug Ketalar® Injection of Parke-Davis.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

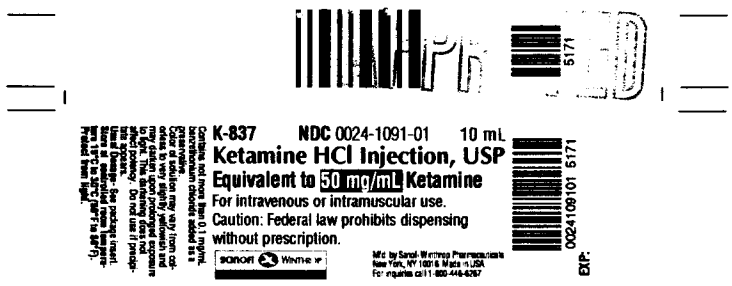
/S/ 6/27/96

Douglas L. Spoirn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074549

FINAL PRINTED LABELING


K-837 NDC 0024-1091-01 10 mL
Ketamine HCl Injection, USP
Equivalent to 50 mg/mL Ketamine
For intravenous or intramuscular use.
Caution: Federal law prohibits dispensing without prescription.
sanofi Winthrop
Mfd. by Sanofi Winthrop Pharmaceuticals
New York, NY 10016 Made in USA
For inquiries call 1-800-446-6267
0024109101 5171
EXP:

JUN 27 1996

K-837 NDC 0024-1091-01 10 Vials 10 mL

KETAMINE HCl INJECTION, USP

Equivalent to 50 mg/mL Ketamine

For intravenous or intramuscular use.

Contains not more than 0.1 mg/mL benzethonium chloride added as a preservative.

Color of solution may vary from colorless to very slightly yellowish and may darken upon prolonged exposure to light. This darkening does not affect potency. Do not use if precipitate appears.

Keep this and all drugs out of the reach of children.

Usual Dosage- See package insert for complete prescribing information.

Store at controlled room temperature 15°C to 30°C (59°F to 86°F).

sanofi WINTHROP

Manufactured by Sanofi Winthrop Pharmaceuticals
New York, NY 10016
For inquiries call 1-800-446-6267

Made in USA

APPROV

JUN 27 1996

PMS 347
PMS Proc. Black
PMS Proc. Blue

K-837 NDC 0024-1091-01 10 mL

KETAMINE HCl
INJECTION, USP

Equivalent to
50 mg/mL
Ketamine

K-837 NDC 0024-1091-01 10 Vials

KETAMINE HCl INJECTION, USI

Equivalent to 50 mg/mL Ketamin

For intravenous or intramuscular use.

Protect from light.

Caution: Federal law prohibits dispensing without prescription.

sanofi WINTHROP

K-837 NDC 0024-1091-01 10 Vials 10 mL

KETAMINE HCl INJECTION, USP

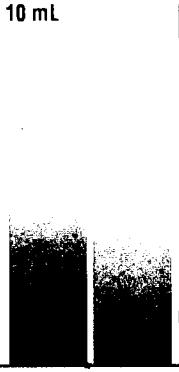
Equivalent to 50 mg/mL Ketamine

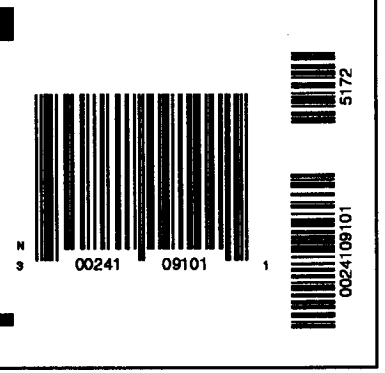
For intravenous or intramuscular use.

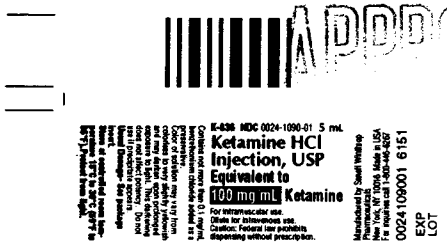
Protect from light.

Caution: Federal law prohibits dispensing without prescription.

sanofi WINTHROP






APPD
E-836 NDC 0024-1090-01 5 mL
Ketamine HCl
Injection, USP
Equivalent to
100 mg/mL Ketamine
For intramuscular use.
Dilute for intravenous use.
Caution: Federal law prohibits
dispensing without prescription.
Manufactured by Sanofi Winthrop
Pharmaceuticals
New York, NY 10004. Made in USA
For revised package see NDC
0024-1090-01 6151
EXP
LOT

JUN 27 1996

APPROVED JUL 27 1996

K-836 NDC 0024-1090-01 10 Vials 5 mL

KETAMINE HCl INJECTION, USP
Equivalent to 100 mg/mL Ketamine

PMS 347
PMS Proc. Black
PMS Proc. Blue

K-836 NDC 0024-1090-01 10 Vials 5 mL

KETAMINE HCl INJECTION, USP
Equivalent to 100 mg/mL Ketamine

For intramuscular use. For intravenous use (with proper dilution).
Contains not more than 0.1 mg/mL benzethonium chloride added as a preservative.
Color of solution may vary from colorless to very slightly yellowish and may darken upon prolonged exposure to light. This darkening does not affect potency. Do not use if precipitate appears.
Keep this and all drugs out of the reach of children.
Usual Dosage- See package insert for complete prescribing information.
Store at controlled room temperature 15°C to 30°C (59°F to 86°F).

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Manufactured by Sanofi Winthrop Pharmaceuticals
New York, NY 10016 Made in USA
For inquiries call 1-800-446-6267

K-836 NDC 0024-1090-01 5 mL

KETAMINE HCl
INJECTION, USP

Equivalent to
100 mg/mL
Ketamine

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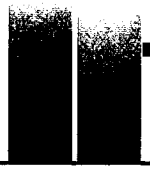

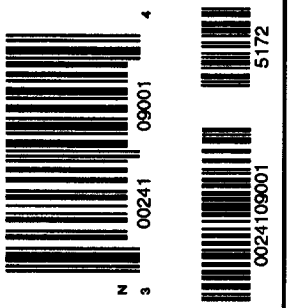

concentration of 50 mg/kg of HLP. These observations support the hypothesis that the hypertension produced by ketamine is due to selective activation of central cardiac stimulating mechanisms leading to an increase in cardiac output. The dog myocardium is not sensitized to epinephrine and ketamine appears to have a weak antiarrhythmic activity.

Metabolic Disposition

Ketamine is rapidly absorbed following parenteral administration. Animal experiments indicated that ketamine was rapidly distributed into body tissues, with relatively high concentrations appearing in body fat, liver, lung, and brain; lower concentrations were found in the heart, skeletal muscle, and blood plasma. Placental transfer of the drug was found to occur in pregnant dogs and monkeys. No significant degree of binding to serum albumin was found with ketamine.

Balance studies in rats, dogs, and monkeys resulted in the recovery of 85% to 95% of the dose in the urine, mainly in the form of degradation products. Small amounts of drug were also excreted in the bile and feces. Balance studies with tritium-labeled ketamine in human subjects (1 mg/lb given intravenously) resulted in the mean recovery of 91% of the dose in the urine and 3% in the feces. Peak plasma levels averaged about 0.75 mcg/mL, and CSF levels were about 0.2 mcg/mL, 1 hour after dosing.

Ketamine undergoes N-demethylation and hydroxylation of the cyclohexanone ring, with the formation of water-soluble conjugates which are excreted in the urine. Further oxidation also occurs with the formation of a cyclohexanone derivative. The unconjugated N-demethylated metabolite was found to be less than one-sixth as potent as ketamine. The unconjugated demethyl cyclohexanone derivative was found to be less than one-tenth as potent as ketamine. Repeated doses of ketamine administered to animals did not produce any detectable increase in microsomal enzyme activity.

Reproduction

Male and female rats, when given five times the average human intravenous dose of ketamine for three consecutive days about one week before mating, had a reproductive performance equivalent to that of saline-injected controls. When given to pregnant rats and rabbits intramuscularly at twice the average human intramuscular dose during the respective periods of organogenesis, the litter characteristics were equivalent to those of saline-injected controls. A small group of rabbits was given a single large dose (six times the average human dose) of ketamine on Day 6 of pregnancy to simulate the effect of an excessive clinical dose around the period of nidation. The outcome of pregnancy was equivalent in control and treated groups.

To determine the effect of ketamine on the perinatal and postnatal period, pregnant rats were given twice the average human intramuscular dose during Days 18 to 21 of pregnancy. Litter characteristics at birth and through the weaning period were equivalent to those of the control animals. There was a slight increase in incidence of delayed parturition by one day in treated dams of this group. Three groups each of mated beagle bitches were given 2.5 times the average human intramuscular dose twice weekly for the three weeks of the first, second, and third trimesters of pregnancy, respectively, without the development of adverse effects in the pups.

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New York, NY 10016

10916151

KETAMINE HYDROCHLORIDE INJECTION, USP

SPECIAL NOTE

EMERGENCE REACTIONS HAVE OCCURRED IN APPROXIMATELY 12 PERCENT OF PATIENTS.

THE PSYCHOLOGICAL MANIFESTATIONS VARY IN SEVERITY BETWEEN PLEASANT DREAM-LIKE STATES, VIVID IMAGERY, HALLUCINATIONS, AND EMERGENCE DELIRIUM. IN SOME CASES THESE STATES HAVE BEEN ACCOMPANIED BY CONFUSION, EXCITEMENT, AND IRRATIONAL BEHAVIOR WHICH A FEW PATIENTS RECALL AS AN UNPLEASANT EXPERIENCE. THE DURATION ORDINARILY IS NO MORE THAN A FEW HOURS; IN A FEW CASES, HOWEVER, RECURRENCES HAVE TAKEN PLACE UP TO 24 HOURS POSTOPERATIVELY. NO RESIDUAL PSYCHOLOGICAL EFFECTS ARE KNOWN TO HAVE RESULTED FROM USE OF KETAMINE.

THE INCIDENCE OF THESE EMERGENCE PHENOMENA IS LEAST IN THE YOUNG (15 YEARS OF AGE OR LESS) AND ELDERLY (OVER 65 YEARS OF AGE) PATIENT. ALSO, THEY ARE LESS FREQUENT WHEN THE DRUG IS GIVEN INTRAMUSCULARLY AND THE INCIDENCE IS REDUCED AS EXPERIENCE WITH THE DRUG IS GAINED.

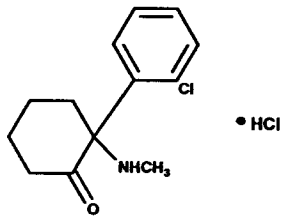
THE INCIDENCE OF PSYCHOLOGICAL MANIFESTATIONS DURING EMERGENCE, PARTICULARLY DREAM-LIKE OBSERVATIONS AND EMERGENCE DELIRIUM, MAY BE REDUCED BY USING LOWER RECOMMENDED DOSAGES OF KETAMINE IN CONJUNCTION WITH INTRAVENOUS DIAZEPAM DURING INDUCTION AND MAINTENANCE OF ANESTHESIA. (See DOSAGE AND ADMINISTRATION.) ALSO, THESE REACTIONS MAY BE REDUCED IF VERBAL, TACTILE AND VISUAL STIMULATION OF THE PATIENT IS MINIMIZED DURING THE RECOVERY PERIOD. THIS DOES NOT PRECLUDE THE MONITORING OF VITAL SIGNS.

IN ORDER TO TERMINATE A SEVERE EMERGENCE REACTION THE USE OF A SMALL HYPNOTIC DOSE OF A SHORT-ACTING OR ULTRASHORT-ACTING BARBITURATE MAY BE REQUIRED.

WHEN KETAMINE IS USED ON AN OUTPATIENT BASIS, THE PATIENT SHOULD NOT BE RELEASED UNTIL RECOVERY FROM ANESTHESIA IS COMPLETE AND THEN SHOULD BE ACCOMPANIED BY A RESPONSIBLE ADULT.

DESCRIPTION

Ketamine hydrochloride is a nonbarbiturate anesthetic chemically designated (±)-2-(*o*-Chlorophenyl)-2-(methylamino) cyclohexanone hydrochloride. It is formulated as a slightly acid (pH 3.5-5.5) sterile solution for intravenous or intramuscular injection in concentrations containing the equivalent of either 50 or 100 mg ketamine base per milliliter and contains not more than 0.1 mg/mL benzethonium chloride added as a preservative. Ketamine hydrochloride has a molecular formula of $C_{13}H_{16}ClNO \cdot HCl$, a molecular weight of 274.19 and the following structural formula:



CLINICAL PHARMACOLOGY

Ketamine is a rapid-acting general anesthetic producing an anesthetic state characterized by profound analgesia, normal pharyngeal-laryngeal reflexes, normal or slightly enhanced skeletal muscle tone, cardiovascular and respiratory stimulation, and occasionally a transient and minimal respiratory depression.

A patent airway is maintained partly by virtue of unimpaired pharyngeal and laryngeal reflexes. (See WARNINGS and PRECAUTIONS.)

The biotransformation of ketamine includes N-dealkylation (metabolite I), hydroxylation of the cyclohexone ring (metabolites III and IV), conjugation with glucuronic acid and dehydration of the hydroxylated metabolites to form the cyclohexene derivative (metabolite II).

Following intravenous administration, the ketamine concentration has an initial slope (alpha phase) lasting about 45 minutes with a half-life of 10 to 15 minutes. This first phase corresponds clinically to the anesthetic effect of the drug. The anesthetic action is terminated by a combination of redistribution from the CNS to slower equilibrating peripheral tissues and by hepatic biotransformation to metabolite I. This metabolite is about 1/3 as active as ketamine in reducing halothane requirements (MAC) of the rat. The later half-life of ketamine (beta phase) is 2.5 hours.

The anesthetic state produced by ketamine has been termed "dissociative anesthesia" in that it appears to selectively interrupt association pathways of the brain before producing somesthetic sensory blockade. It may selectively depress the thalamoneocortical system before significantly obtunding the more ancient cerebral centers and pathways (reticular-activating and limbic systems).

Elevation of blood pressure begins shortly after injection, reaches a maximum within a few minutes and usually returns to preanesthetic values within 15 minutes after injection. In the majority of cases, the systolic and diastolic blood pressure peaks from 10% to 50% above preanesthetic levels shortly after induction of anesthesia, but the elevation can be higher or longer in individual cases (see CONTRAINDICATIONS).

Ketamine has a wide margin of safety; several instances of unintentional administration of overdoses of ketamine (up to ten times that usually required) have been followed by prolonged but complete recovery.

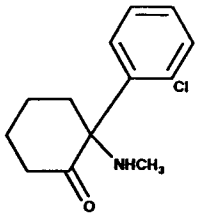
Ketamine has been studied in over 12,000 operative and diagnostic procedures, involving over 10,000 patients from 105 separate studies. During the course of these studies ketamine hydrochloride was administered as the sole agent, as induction for other general agents, or to supplement low-potency agents.

Specific areas of application have included the following:

1. debridement, painful dressings, and skin grafting in burn patients, as well as other superficial surgical procedures.
2. neurodiagnostic procedures such as pneumonencephalograms, ventriculograms, myelograms, and lumbar punctures. See also PRECAUTION concerning increased intracranial pressure.
3. diagnostic and operative procedures of the eye, ear, nose, and mouth, including dental extractions.
4. diagnostic and operative procedures of the pharynx, larynx, or bronchial tree. NOTE: Muscle relaxants, with proper attention to respiration, may be required (see PRECAUTIONS).
5. sigmoidoscopy and minor surgery of the anus and rectum, and circumcision.
6. extraperitoneal procedures used in gynecology such as dilatation and curettage.
7. orthopedic procedures such as closed reductions, manipulations, femoral pinning, amputations, and biopsies.
8. as an anesthetic in poor risk patients with depression of vital functions

mesters of pregnancy, respectively, without the development of adverse effects the pups.

formula:



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New York, NY 10016

10916151

CLINICAL PHARMACOLOGY

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Elevation of blood pressure begins shortly after injection, reaches a maximum within a few minutes and usually returns to preanesthetic values within 15 minutes after injection. In the majority of cases, the systolic and diastolic blood pressure peaks from 10% to 50% above preanesthetic levels shortly after induction of anesthesia, but the elevation can be higher or longer in individual cases (see CONTRAINDICATIONS).

Ketamine has a wide margin of safety; several instances of unintentional administration of overdoses of ketamine (up to ten times that usually required) have been followed by prolonged but complete recovery.

Ketamine has been studied in over 12,000 operative and diagnostic procedures, involving over 10,000 patients from 105 separate studies. During the course of these studies ketamine hydrochloride was administered as the sole agent, as induction for other general agents, or to supplement low-potency agents.

Specific areas of application have included the following:

1. debridement, painful dressings, and skin grafting in burn patients, as well as other superficial surgical procedures.
2. neurodiagnostic procedures such as pneumonencephalograms, ventriculograms, myelograms, and lumbar punctures. See also PRECAUTION concerning increased intracranial pressure.
3. diagnostic and operative procedures of the eye, ear, nose, and mouth, including dental extractions.
4. diagnostic and operative procedures of the pharynx, larynx, or bronchial tree. NOTE: Muscle relaxants, with proper attention to respiration, may be required (see PRECAUTIONS).
5. sigmoidoscopy and minor surgery of the anus and rectum, and circumcision.
6. extraperitoneal procedures used in gynecology such as dilatation and curettage.
7. orthopedic procedures such as closed reductions, manipulations, femoral pinning, amputations, and biopsies.
8. as an anesthetic in poor-risk patients with depression of vital functions.
9. in procedures where the intramuscular route of administration is preferred.
10. in cardiac catheterization procedures.

In these studies, the anesthesia was rated either "excellent" or "good" by the anesthesiologist and the surgeon at 90% and 93%, respectively; rated "fair" at 6% and 4%, respectively; and rated "poor" at 4% and 3%, respectively. In a second method of evaluation, the anesthesia was rated "adequate" in at least 90% and "inadequate" in 10% or less of the procedures.

Printed in USA Revised March 1996
KSW-2A

INDICATIONS AND USAGE

Ketamine hydrochloride injection is indicated as the sole anesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation. Ketamine hydrochloride injection is best suited for short procedures but it can be used, with additional doses, for longer procedures.

Ketamine hydrochloride injection is indicated for the induction of anesthesia prior to the administration of other general anesthetic agents.

Ketamine hydrochloride injection is indicated to supplement low-potency agents, such as nitrous oxide.

Specific areas of application are described in the CLINICAL PHARMACOLOGY section.

CONTRAINDICATIONS

Ketamine is contraindicated in those in whom a significant elevation of blood pressure would constitute a serious hazard and in those who have shown hypersensitivity to the drug.

WARNINGS

Cardiac function should be continually monitored during the procedure in patients found to have hypertension or cardiac decompensation.

Postoperative confusional states may occur during the recovery period. (See SPECIAL NOTE.)

Respiratory depression may occur with overdosage or too rapid a rate of administration of ketamine, in which case supportive ventilation should be employed. Mechanical support of respiration is preferred to administration of analeptics.

PRECAUTIONS

General

Ketamine should be used by or under the direction of physicians experienced in administering general anesthetics and in maintenance of an airway and in the control of respiration.

Because pharyngeal and laryngeal reflexes are usually active, ketamine should not be used alone in surgery or diagnostic procedures of the pharynx, larynx, or bronchial tree. Mechanical stimulation of the pharynx should be avoided, whenever possible, if ketamine is used alone. Muscle relaxants, with proper attention to respiration, may be required in both of these instances.

Resuscitative equipment should be ready for use.

The incidence of emergence reactions may be reduced if verbal and tactile stimulation of the patient is minimized during the recovery period. This does not preclude the monitoring of vital signs (see SPECIAL NOTE).

The intravenous dose should be administered over a period of 60 seconds. More rapid administration may result in respiratory depression or apnea and enhanced pressor response.

In surgical procedures involving visceral pain pathways, ketamine should be supplemented with an agent which obtunds visceral pain.

Use with caution in the chronic alcoholic and the acutely alcohol-intoxicated patient.

An increase in cerebrospinal fluid pressure has been reported following administration of ketamine. Use with extreme caution in patients with preanesthetic elevated cerebrospinal fluid pressure.

Information for Patients

As appropriate, especially in cases where early discharge is possible, the duration of ketamine and other drugs employed during the conduct of anesthesia should be considered. The patients should be cautioned that driving an automobile, operating hazardous machinery or engaging in hazardous activities should not be undertaken for 24 hours or more (depending upon the dosage of ketamine and consideration of other drugs employed) after anesthesia.

Drug Interactions

Prolonged recovery time may occur if barbiturates and/or narcotics are used concurrently with ketamine.

Ketamine is clinically compatible with the commonly used general and local anesthetic agents when an adequate respiratory exchange is maintained.

Usage in Pregnancy

Since the safe use in pregnancy, including obstetrics (either vaginal or abdominal delivery), has not been established, such use is not recommended (see ANIMAL PHARMACOLOGY AND TOXICOLOGY, Reproduction).

ADVERSE REACTIONS

Cardiovascular

Blood pressure and pulse rate are frequently elevated following administration of ketamine alone. However, hypotension and bradycardia have been observed. Arrhythmia has also occurred.

Respiration

Although respiration is frequently stimulated, severe depression of respiration or apnea may occur following rapid intravenous administration of high doses of ketamine. Laryngospasms and other forms of airway obstruction have occurred during ketamine anesthesia.

Eye

Diplopia and nystagmus have been noted following ketamine administration. It also may cause a slight elevation in intraocular pressure measurement.

Psychological: (See SPECIAL NOTE.)

Neurological

In some patients, enhanced skeletal muscle tone may be manifested by tonic and clonic movements sometimes resembling seizures (see DOSAGE AND ADMINISTRATION).

Gastrointestinal

Anorexia, nausea and vomiting have been observed; however, this is not usually severe and allows the great majority of patients to take liquids by mouth shortly after regaining consciousness (see DOSAGE AND ADMINISTRATION).

General

Local pain and exanthema at the injection site have infrequently been reported. Transient erythema and/or morbilliform rash have also been reported.

OVERDOSAGE

Respiratory depression may occur with overdosage or too rapid a rate of administration of ketamine, in which case supportive ventilation should be employed. Mechanical support of respiration is preferred to administration of analeptics.

DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Note: Barbiturates and ketamine, being chemically incompatible because of precipitate formation, *should not* be injected from the same syringe.

If the ketamine dose is augmented with diazepam, the two drugs must be given separately. Do not mix ketamine hydrochloride and diazepam in syringe or infusion flask. For additional information on the use of diazepam, refer to the WARNINGS and DOSAGE AND ADMINISTRATION sections of the diazepam insert.

Preoperative Preparations

Onset and Duration

Because of rapid induction following the initial intravenous injection, the patient should be in a supported position during administration.

The onset of action of ketamine is rapid; an intravenous dose of 2 mg/kg (1 mg/lb) of body weight usually produces surgical anesthesia within 30 seconds after injection, with the anesthetic effect usually lasting five to ten minutes. If a longer effect is desired, additional increments can be administered intravenously or intramuscularly to maintain anesthesia without producing significant cumulative effects.

Intramuscular doses, from experience primarily in children, in a range of 9 to 13 mg/kg (4 to 6 mg/lb) usually produce surgical anesthesia within 3 to 4 minutes following injection, with the anesthetic effect usually lasting 12 to 25 minutes.

Dosage

As with other general anesthetic agents, the individual response to ketamine is somewhat varied depending on the dose, route of administration, and age of patient, so that dosage recommendation cannot be absolutely fixed. The drug should be titrated against the patient's requirements.

Induction

Intravenous Route: The initial dose of ketamine administered intravenously may range from 1 mg/kg to 4.5 mg/kg (0.5 to 2 mg/lb). The average amount required to produce five to ten minutes of surgical anesthesia has been 2 mg/kg (1 mg/lb).

Alternatively, in adult patients an induction dose of 1 mg to 2 mg/kg intravenous ketamine at a rate of 0.5 mg/kg/min may be used for induction of anesthesia. In addition, diazepam in 2 mg to 5 mg doses, administered in a separate syringe over 60 seconds, may be used. In most cases, 15 mg of intravenous diazepam *or less* will suffice. The incidence of psychological manifestations during emergence, particularly dream-like observations and emergence delirium, may be reduced by this induction dosage program.

Note: The 100 mg/mL concentration of ketamine *should not* be injected intravenously without proper dilution. It is recommended the drug be diluted with an equal volume of either Sterile Water for Injection, Sodium Chloride Injection, 0.9% or Dextrose Injection, 5%.

Rate of Administration: It is recommended that ketamine be administered slowly (over a period of 60 seconds). More rapid administration may result in respiratory depression and enhanced pressor response.

Intramuscular Route: The initial dose of ketamine administered intramuscularly may range from 6.5 to 13 mg/kg (3 to 6 mg/lb). A dose of 10 mg/kg (5 mg/lb) will usually produce 12 to 25 minutes of surgical anesthesia.

Maintenance of Anesthesia

The maintenance dose should be adjusted according to the patient's anesthetic needs and whether an additional anesthetic agent is employed.

Increments of one-half to the full induction dose may be repeated as needed for maintenance of anesthesia. However, it should be noted that purposeless and tonic-clonic movements of extremities may occur during the course of anesthesia. These movements do not imply a light plane and are not indicative of the need for additional doses of the anesthetic.

It should be recognized that the larger the total dose of ketamine administered, the longer will be the time to complete recovery.

Adult patients induced with ketamine augmented with intravenous diazepam may be maintained on ketamine given by slow microdrip infusion technique at a dose of 0.1 to 0.5mg/minute, augmented with diazepam 2 to 5 mg administered intravenously as needed. In many cases 20 mg or *less* of intravenous diazepam total for combined induction and maintenance will suffice. However, slightly more diazepam may be required depending on the nature and duration of the operation, physical status of the patient, and other factors. The incidence of psychological manifestations during emergence, particularly dream-like observations and emergence delirium, may be reduced by this maintenance dosage program.

Dilution: To prepare a dilute solution containing 1 mg of ketamine per mL, aseptically transfer 10 mL (50 mg per mL vial) or 5 mL (100 mg per mL vial) to 500 mL of Dextrose Injection, 5% or Sodium Chloride Injection, 0.9% and mix well. The resultant solution will contain 1 mg of ketamine per mL.

The fluid requirements of the patient and duration of anesthesia must be considered when selecting the appropriate dilution of ketamine hydrochloride injection. If fluid restriction is required, ketamine hydrochloride injection can be added to a 250 mL infusion as described above to provide a ketamine concentration of 2 mg/mL.

Supplementary Agents

Ketamine is clinically compatible with the commonly used general and local anesthetic agents when an adequate respiratory exchange is maintained.

The regimen of a reduced dose of ketamine supplemented with diazepam can be used to produce balanced anesthesia by combination with other agents such as nitrous oxide and oxygen.

HOW SUPPLIED

Ketamine Hydrochloride Injection, USP is supplied as the hydrochloride in concentrations equivalent to ketamine base.

50 mg/mL, 10 mL vial, box of 10 (NDC 0024-1091-01).

100 mg /mL, 5 mL vial, box of 10 (NDC 0024-1090-01).

Color of solution may vary from colorless to very slightly yellowish and may darken upon prolonged exposure to light. This darkening does not affect potency. Do not use if a precipitate appears.

Store at controlled room temperature 15° C to 30° C (59° F to 86° F).

Protect from light.

Caution: Federal law prohibits dispensing without prescription.

ANIMAL PHARMACOLOGY AND TOXICOLOGY

Toxicity

The acute toxicity of ketamine has been studied in several species. In mature mice and rats, the intraperitoneal LD_{50} values are approximately 100 times the average human intravenous dose and approximately 20 times the average human intramuscular dose. A slightly higher acute toxicity observed in neonatal rats was not sufficiently elevated to suggest an increased hazard when used in children. Daily intravenous injections in rats of five times the average human intravenous dose and intramuscular injections in dogs at four times the average human intramuscular dose demonstrated excellent tolerance for as long as 6 weeks. Similarly, twice weekly anesthetic sessions of one, three, or six hours' duration in monkeys over a four- to six-week period were well tolerated.

Interaction with other Drugs Commonly Used for Preanesthetic Medication

Large doses (three or more times the equivalent effective human dose) of morphine, meperidine, and atropine increased the depth and prolonged the duration of anesthesia produced by a standard anesthetizing dose of ketamine in Rhesus monkeys. The prolonged duration was not of sufficient magnitude to contraindicate the use of these drugs for preanesthetic medication in human clinical trials.

Blood Pressure

Blood pressure responses to ketamine vary with the laboratory species and experimental conditions. Blood pressure is increased in normotensive and renal hypertensive rats with and without adrenalectomy and under pentobarbital anesthesia.

Intravenous ketamine produces a fall in arterial blood pressure in the Rhesus monkey and a rise in arterial blood pressure in the dog. In this respect the dog mimics the cardiovascular effect observed in man. The pressor response to

supplemented with an agent which obtunds visceral pain.

Use with caution in the chronic alcoholic and the acutely alcohol-intoxicated patient.

An increase in cerebrospinal fluid pressure has been reported following administration of ketamine. Use with extreme caution in patients with preanesthetic elevated cerebrospinal fluid pressure.

Information for Patients

As appropriate, especially in cases where early discharge is possible, the duration of ketamine and other drugs employed during the conduct of anesthesia should be considered. The patients should be cautioned that driving an automobile, operating hazardous machinery or engaging in hazardous activities should not be undertaken for 24 hours or more (depending upon the dosage of ketamine and consideration of other drugs employed) after anesthesia.

Drug Interactions

Prolonged recovery time may occur if barbiturates and/or narcotics are used concurrently with ketamine.

Ketamine is clinically compatible with the commonly used general and local anesthetic agents when an adequate respiratory exchange is maintained.

Usage in Pregnancy

Since the safe use in pregnancy, including obstetrics (either vaginal or abdominal delivery), has not been established, such use is not recommended (see ANIMAL PHARMACOLOGY AND TOXICOLOGY, Reproduction).

ADVERSE REACTIONS

Cardiovascular

Blood pressure and pulse rate are frequently elevated following administration of ketamine alone. However, hypotension and bradycardia have been observed. Arrhythmia has also occurred.

Respiration

Although respiration is frequently stimulated, severe depression of respiration or apnea may occur following rapid intravenous administration of high doses of ketamine. Laryngospasms and other forms of airway obstruction have occurred during ketamine anesthesia.

Eye

Diplopia and nystagmus have been noted following ketamine administration. It also may cause a slight elevation in intraocular pressure measurement.

Psychological: (See SPECIAL NOTE.)

Neurological

In some patients, enhanced skeletal muscle tone may be manifested by tonic and clonic movements sometimes resembling seizures (see DOSAGE AND ADMINISTRATION).

Gastrointestinal

Anorexia, nausea and vomiting have been observed; however, this is not usually severe and allows the great majority of patients to take liquids by mouth shortly after regaining consciousness (see DOSAGE AND ADMINISTRATION).

General

Local pain and exanthema at the injection site have infrequently been reported. Transient erythema and/or morbilliform rash have also been reported.

OVERDOSAGE

Respiratory depression may occur with overdosage or too rapid a rate of administration of ketamine, in which case supportive ventilation should be employed. Mechanical support of respiration is preferred to administration of analeptics.

DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Note: Barbiturates and ketamine, being chemically incompatible because of precipitate formation, *should not* be injected from the same syringe.

If the ketamine dose is augmented with diazepam, the two drugs must be given separately. Do not mix ketamine hydrochloride and diazepam in syringe or infusion flask. For additional information on the use of diazepam, refer to the WARNINGS and DOSAGE AND ADMINISTRATION sections of the diazepam insert.

Preoperative Preparations

1. While vomiting has been reported following ketamine administration, some airway protection may be afforded because of active laryngeal-pharyngeal reflexes. However, since aspiration may occur with ketamine and since protective reflexes may also be diminished by supplementary anesthetics and muscle relaxants, the possibility of aspiration must be considered. Ketamine is recommended for use in the patient whose stomach is not empty when, in the judgment of the practitioner, the benefits of the drug outweigh the possible risks.

2. Atropine, scopolamine, or another drying agent should be given at an appropriate interval prior to induction.

tonic-clonic movements of extremities may occur during the course of anesthesia. These movements do not imply a light plane and are not indicative of the need for additional doses of the anesthetic.

It should be recognized that the larger the total dose of ketamine administered, the longer will be the time to complete recovery.

Adult patients induced with ketamine augmented with intravenous diazepam may be maintained on ketamine given by slow microdrip infusion technique at a dose of 0.1 to 0.5mg/minute, augmented with diazepam 2 to 5 mg administered intravenously as needed. In many cases 20 mg or *less* of intravenous diazepam total for combined induction and maintenance will suffice. However, slightly more diazepam may be required depending on the nature and duration of the operation, physical status of the patient, and other factors. The incidence of psychological manifestations during emergence, particularly dream-like observations and emergence delirium, may be reduced by this maintenance dosage program.

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Blood Pressure

Blood pressure responses to ketamine vary with the laboratory species and experimental conditions. Blood pressure is increased in normotensive and renal hypertensive rats with and without adrenalectomy and under pentobarbital anesthesia.

Intravenous ketamine produces a fall in arterial blood pressure in the Rhesus monkey and a rise in arterial blood pressure in the dog. In this respect the dog mimics the cardiovascular effect observed in man. The pressor response to ketamine injected into intact, unanesthetized dogs is accompanied by a tachycardia, rise in cardiac output and a fall in total peripheral resistance. It causes a fall in perfusion pressure following a large dose injected into an artificially perfused vascular bed (dog hindquarters), and it has little or no potentiating effect upon vasoconstriction responses of epinephrine or norepinephrine. The pressor response to ketamine is reduced or blocked by chlorpromazine (central depressant and peripheral α-adrenergic blockade), by β-adrenergic blockade, and by ganglionic blockade. The tachycardia and increase in myocardial contractile force seen in intact animals does not appear in isolated hearts (Langendorff) at a concentration of 0.1 mg of ketamine nor in Starling dog heart-lung preparations at a ketamine

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074549

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 74-549

3. NAME AND ADDRESS OF APPLICANT
Sanofi Winthrop, Inc.
Attention: Linda L. Nardone, Ph.D.
90 Park Avenue
New York, NY 10016

4. BASIS OF SUBMISSION
The patent for the innovator's Ketalar is expired and there is no marketing exclusivity period in force for the subject drug product under Section 505(j)(4)(D) of the Act.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Ketamine Hydrochloride

8. SUPPLEMENT PROVIDE FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

September 30, 1994--	Original Submission
October 25, 1994--	Acknowledgement Receipt
November 4, 1994--	Transfer of ownership letter
December 30, 1994--	Chemistry Review No. 1
January 9, 1995--	Micro Review No. 1
February 3, 1995--	Bio waiver granted
March 10, 1995--	Deficiency letter
June 16, 1995--	ANDA Amendment
September 13, 1996--	Deficiency letter
April 19, 1996--	ANDA Amendment

10. PHARMACOLOGICAL CATEGORY
Anesthetic

11. Rx or OTC
Rx

12. RELATED Drug Master Files

(b)4 - Confidential Business

13. DOSAGE FORM
Injection

14. POTENCY
50 mg & 100 mg base/mL

15. CHEMICAL NAME AND STRUCTURE
Cyclohexanone, 2-(2-chlorophenyl)-2-(methylamino)-hydrochloride. Molecular weights: Hcl 274.19; base 237.17.

16. RECORDS AND REPORTS
N/A

17. COMMENTS
A justification for the residual solvents [redacted] is appended. This amendment was triggered by [redacted] per reviewer's request. The residual solvents limits are acceptable since the listed solvents are considered to be of low risk to human health.

(b)4 - Confidential Business

18. CONCLUSIONS AND RECOMMENDATIONS
Recommend approval letter to issue.

19. REVIEWER:
[redacted]
/S/

DATE COMPLETED:
May 2, 1996
5/30/96

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074549

BIOEQUIVALENCE REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 74-549 SPONSOR: Sterling Winthrop, I
DRUG: Ketamine HCL
DOSAGE FORM: Injection
STRENGTH(s): 50 mg Base/mL and 100 mg Base/mL
TYPE OF STUDY: Single/Multiple Fasting/Fed
STUDY SITE:

STUDY SUMMARY: N/A

In-vivo bioequivalence study requirements waived per 21 CFR 320.22(b)(1). Formulation of test product identical to that of reference listed drug, Ketalar®, manufactured by Parke-Davis.

DISSOLUTION: N/A

PRIMARY REVIEWER: J. A. Quidenkirk BRANCH: I

INITIA(b)4 - Confidential Business DATE: 6-11-96

BRANCH CHIEF: Y. C. Huang BRANCH: I

INITIAL: (b)4 - Confidential Business DATE: 6/12/96

DIRECTOR
DIVISION OF BIOEQUIVALENCE

INITIAL: (b)4 - Confidential Business DATE: 6/12/96

DIRECTOR
OFFICE OF GENERIC DRUGS

INITIAL: (b)4 - Confidential Business DATE: 6/12/96

FEB 3 1995

Ketamine HCL
Injection, 50 and 100 mg base/mL
ANDA #74-549
Reviewer: L.A.Ouderkirk
WP No. 74549W.994

Sterling Winthrop, Inc.
New York, New York
Submission Dated:
September 30, 1994

Review of a Waiver Request for an Injectable Dosage Form

The firm has requested that the in-vivo bioequivalence requirements for its ketamine HCL injection, 50 mg base/mL and 100 mg base/mL be waived per 21 CFR 320.22 (b)(1). The listed reference product is Ketalar® injection, sponsored by Parke-Davis. Sterling Winthrop states that its product, when approved, will be marketed by Kanetta Pharmacal, an affiliated firm. The product will be manufactured at a [redacted](b)4 - Confidential[redacted] The formulations for the test and reference products are listed in Table 1, below:

TABLE 1	STERLING WINTHROP		PARK-DAVIS	
INGREDIENT	50 MG/ML	100 MG/ML	50 MG/ML	100MG/ML
Ketamine HCL, USP	57.7 mg	115.3 mg	57.7 mg*	115.3 mg
Benzethonium Chloride, USP	0.100 mg	0.100 mg	0.100 mg	0.100 mg
Water for Injection, USP	q.s.	q.s.	q.s.	q.s.

Comment:

The firm has met the criteria for waiver of the in-vivo bioequivalence study requirements for its ketamine HCL injection, 50 mg base/mL and 100 mg base/mL per 21 CFR 320.22 (b)(1), as follows:

(i) The drug product is a parenteral solution intended solely for administration by injection, and,

(ii) It contains the same active and inactive ingredients in the same concentration as the approved reference product.

Recommendations:

1. The waiver of in-vivo bioequivalence study requirements for the firm's ketamine HCL injection, 50 mg base/mL and 100 mg base/mL is granted per 21 CFR 320.22(b)(1). The 50 mg base/mL and 100 mg base/mL strengths of the test product are therefore deemed bioequivalent to the identical strengths of Ketalar® injection, sponsored by Parke-Davis.

2. From the bioequivalence viewpoint, the firm has met the bioequivalence requirements and the ANDA #74-549 is acceptable.

/S/

Larry A. Ouderkirk
Division of Bioequivalence
Review Branch 1

RM

RD INITIALED RMMHATRE
FT INITIALED RMMHATRE

/S/ Date: 2/3/95

cc: ANDA 74-549 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-130 (JAllen), HFD-652 (Mhatre, Ouderkirk), Drug File, Division File

LAO/020295/ntp/WP#74549W.994